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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)


(51) International Patent Classification 6 :
A61K 31/44 // (A61K 31/44, 31:215) (A61K 31/44, 31:19) (A61K 31/44, 31:35) (A61K 31/44, 31:22) (A61K 31/44, 31:44)

A1

(11) International Publication Number: WO 97/35576

(43) International Publication Date: 2 October 1997 (02.10.97)

(21) International Application Number: PCT/IL97/00085

(22) International Filing Date: 10 March 1997 (10.03.97)

(30) Priority Data:
117702 28 March 1996 (28.03.96) IL



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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
*With international search report.*
*With amended claims and statement.*


(54) Title: USE OF ISONIAZID FOR THE TREATMENT OF HYPERLIPOPROTEINEMIA


(57) Abstract

The known tuberculosis drug isoniazid (also known as isonicotinic acid hydrazide or INH) has unexpectedly been found to be useful for treating hyperlipoproteinemia. A method for decreasing the low-density lipoprotein/high-density lipoprotein (LDL/HDL) cholesterol ratio in the plasma of a mammal by administering isoniazid tothe mammal is disclosed. Isoniazid can be administrated together with other drugs known to lower the concentration of plasma lipoproteins to obtain an increased effect. A pharmaceutical composition containing isoniazid is also described.

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# USE OF ISONIAZID FOR THE TREATMENT OF HYPERLIPOPROTEINEMIA

## FIELD OF THE INVENTION

The present invention relates to the use of a known drug for the prevention and treatment of hyperlipoproteinemia which can lead to heart disease.

## BACKGROUND OF THE INVENTION

Hyperlipoproteinemia is a condition in which the concentration of cholesterol- and/or triacylglycerol-carrying lipoproteins in the plasma exceeds a well defined normal limit. Clinical concern arises because an elevated concentration of lipoproteins can accelerate the development of atherosclerosis, thrombosis and infarction. Numerous population studies have shown that elevated serum concentration of total cholesterol, and especially low-density lipoprotein (LDL)-cholesterol, constitutes a major risk factor for the occurrence of atherosclerotic events. It has been clearly demonstrated that lowering the concentration of cholesterol-carrying lipoproteins in plasma can diminish the risk of myocardial infarction. However, there is now well established evidence that an increase in high-density lipoprotein (HDL)-cholesterol (and thus a decrease in the LDL/HDL cholesterol ratio) also has a beneficial and protective effect against the development of atherosclerosis and its complications. It is therefore more common to use the LDL/HDL cholesterol ratio as a measure of the plasma lipid profile with respect to predisposition to heart disease.

Various therapeutic measures are currently available in order to improve plasma lipid profile. These include the administration of various

drugs which generally lower the concentration of plasma lipoproteins (Goodman and Gilman. The Pharmacological Basis of Therapeutics, Eighth Edition (1990) Pergamon Press, Inc., Maxwell House, Fairview Park, Elmsford, New York, pg. 881-894) These drugs include:

(1) Fibric Acids: Aryloxyisobutyric acids and other related compounds collectively referred to as fibric acids have been found to be effective in reducing plasma concentrations of triglycerides and LDL-cholesterol. Some of these drugs have also been shown to mildly increase HDL-cholesterol. Among the better known compounds are: clofibrate, gemfibrozil, fenofibrate, ciprofibrate, benzafibrate.

(2) HMG (hydroxymethylglutaric acid) CoA reductase inhibitors: These drugs, which are fungal-derived compounds, were found effective in lowering LDL-cholesterol and generally result in a mild increase in HDL-cholesterol. Compounds include: mevastatin, lovastatin, simvastatin, pravastatin.

(3) Nicotinic Acid: This drug decreases plasma triglycerides, LDL-cholesterol and induce a mild to moderate increase in HDL-cholesterol, but its use is limited by the frequent occurrence of serious side effects.

Most of the aforementioned drugs exert their beneficial effects mainly by reducing LDL-cholesterol. It would be advantageous to also have a drug which acts mainly to increase HDL-cholesterol without causing undue side effects.

Isoniazid, also known as isonicotinic acid hydrazide (INH), is considered to be a primary drug for the chemotherapy of tuberculosis (Goodman and Gilman, *supra*, pages 1146-1149). Other minor therapeutic uses which have been described for this drug include cerebellar tremor, Crohn's Disease, Huntington's Disease, Parkinson's Disease, Multiple Sclerosis and shoulder-hand syndrome. Although its precise anti-tuberculous mechanism is unknown, it was observed to act on the same hepatic enzymes as does alcohol. The latter has been shown to have the capability of increasing plasma HDL-cholesterol.

One study (Tanàlp, R. and Uzalp, B., Ankara Univ. Tip Fak. Mecm. (1978), in Chem. Abst.91(1):243k) showed an increase in blood cholesterol in rats treated with a combination of isoniazid and testosterone propionate. Another study (Manyam, B.V. in Chest 84:120 (1983)) briefly described a decrease in serum cholesterol in humans on treatment with isoniazid. A third study (Krishnamoorthy, M.S. and Karthikoyan, S. Pharmacol Res. (1991) 24(3):219-25) reported an increase in the levels of plasma total lipid and cholesterol in phenobarbitone sodium-pretreated rabbits after INH treatment, while treatment with INH alone did not alter the lipid levels in plasma and tissues.

Thus, there is no clear indication in the literature as to a potential use of isoniazid in treating hyperlipoproteinemia.

## BRIEF SUMMARY OF THE INVENTION

It is an object of the present invention to provide a drug capable of lowering the LDL/HDL plasma cholesterol ratio.

It is a further object of the present invention to provide a drug capable of increasing the HDL-cholesterol level in the plasma.

Additionally, it is an object of the present invention to provide a method of treating hyperlipoproteinemia in a mammal by drug administration.

It has now been surprisingly discovered that the anti-tuberculosis drug isoniazid is active in increasing the HDL cholesterol concentration in the plasma.

According to one aspect of the present invention, there is provided a method for decreasing the LDL/HDL cholesterol ratio in the plasma of a mammal comprising administering isoniazid to the mammal.

Further in accordance with this aspect of the present invention, there is provided a method for decreasing the LDL/HDL cholesterol ratio in the plasma of a mammal wherein the ratio is decreased by an increase in the concentration of HDL-cholesterol in the plasma.

According to another aspect of the present invention, isoniazid is administered in combination with a hypolipidemic drug. The combination of the two drugs results in a lowering of the LDL/HDL ratio and enables utilizing lower doses of each of the individual drugs, thus minimizing drug specific side effects.

According to yet another aspect of the present invention, there is provided a use of isoniazid in the preparation of a pharmaceutical composition capable of decreasing the LDL/HDL cholesterol ratio in the plasma of a mammal.

## DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

The effect of isoniazid in increasing the plasma HDL cholesterol concentration was demonstrated in the following clinical study. Nine apparently healthy individuals (six males and three females) were treated (because of suspected tuberculosis) with 300 mg/day of oral isoniazid for 6 months. Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were determined in serial blood tests taken at baseline, after 3 and 6 months of treatment, and 3 months after termination of the treatment (for which there are currently results for only 4 patients). The tests were carried out using kits (Boehringer Mannheim) based on an enzymatic hydrolysis method which measure triglycerides and cholesterol and HDL. Total cholesterol was calculated according to the Friedwald equation (Friedwald, Y. *et al.* Clin. Chem.. 18:499-502 (1972)).

The results are presented in Tables I-IV:

Table I: HDL-Cholesterol (mg/dl)

| Patient | Age | Sex | Initial | 3 months | 6 months | 3 month Post-treatment |
|---|---|---|---|---|---|---|
| 1 | 69 | F | 69 | 71 | 69 | ... |
| 2 | 58 | F | 40 | 44 | 50 | 42 |
| 3 | 22 | M | 56 | 54 | 59 | ... |
| 4 | 17 | F | 62 | 97 | 98 | 65 |
| 5 | 58 | M | 53 | 44 | 62 | 52 |
| 6 | 50 | M | 68 | 72 | 92 | ... |
| 7 | 73 | M | 40 | 39 | 54 | ... |
| 8 | 38 | M | 57 | 74 | 71 | ... |
| 9 | 43 | M | 47 | 52 | 62 | 49 |

Table II: LDL-Cholesterol (mg/dl)

| Patient | Initial | 3 months | 6 months | 3 months Post-treatment |
|---|---|---|---|---|
| 1 | 103 | 113 | 105 | ... |
| 2 | 132 | 125 | 155 | 42 |
| 3 | 76 | 62 | 92 | ... |
| 4 | 82 | 84 | 90 | 98 |
| 5 | 144 | 123 | 152 | 162 |
| 6 | 80 | 95 | 109 | ... |
| 7 | 134 | 110 | 120 | ... |
| 8 | 151 | 121 | 117 | ... |
| 9 | 99 | 88 | 95 | 129 |

**Table III: Total Cholesterol (mg/dl)**

| Patient | Initial | 3 months | 6 months | 3 month Post-treatment |
|---|---|---|---|---|
| 1 | 209 | 201 | 195 | ... |
| 2 | 228 | 225 | 260 | 234 |
| 3 | 145 | 125 | 164 | ... |
| 4 | 159 | 194 | 199 | 179 |
| 5 | 226 | 191 | 240 | 240 |
| 6 | 162 | 194 | 231 | ... |
| 7 | 229 | 188 | 207 | ... |
| 8 | 245 | 212 | 191 | ... |
| 9 | 183 | 163 | 201 | 196 |

**Table IV: Triglycerides (mg/dl)**

| Patient | Initial | 3 months | 6 months | 3 months Post-Treatment |
|---|---|---|---|---|
| 1 | 184 | 158 | 165 | ... |
| 2 | 280 | 281 | 275 | 428 |
| 3 | 66 | 47 | 64 | ... |
| 4 | 74 | 66 | 54 | 79 |
| 5 | 144 | 121 | 128 | 131 |
| 6 | 71 | 133 | 151 | ... |
| 7 | 276 | 194 | 161 | ... |
| 8 | 185 | 85 | 64 | ... |
| 9 | 161 | 116 | 95 | 129 |

The results are summarized in Table V:

**Table V**

| parameter measured | baseline (n=9) | 6 months (n=9) | p values |
|---|---|---|---|
| HDL-cholesterol | 55±11 | 69±16 | 0.005 |
| LDL-cholesterol | 111±29 | 115±24 | NS |
| total cholesterol | 198±37 | 210±29 | NS |
| triglycerides | 160±82 | 129±70 | 0.165 |

NS - not significant

It may be seen that a significant increase in plasma HDL-cholesterol from 55±11 mg% at baseline to 69±16 mg% at 6 months (p=0.005) was attained. No significant changes were observed in the other parameters.

This clinical study was later broadened to encompass 15 patients. The HDL-cholesterol level was measured at the baseline and after 3 and 6 months of treatment. The results are summarized in Table VI:

**Table VI: HDL-cholesterol (mg/dl)**

| months of treatment | baseline (n=15) | post-treatment (n=15) | p values |
|---|---|---|---|
| 3 | 53±11 | 61±19 | 0.048 |
| 6 | 53±11 | 65±18 | 0.002 |

It can be seen that a significant increase in HDL-cholesterol was obtained with isoniazid treatment already after three months. Thus it can be seen that the administration of isoniazid results in a decrease in the LDL/HDL cholesterol ratio by increasing the HDL-cholesterol concentration.

The ratio can be further decreased by administering a hypolipidemic drug, which decreases the concentration of LDL cholesterol, in combination with isoniazid. Such drugs include fibric acids such as clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate; HMG CoA reductase inhibitors such as mevastatin, lovastatin, simvastatin and pravastatin; and nicotinic acid.

A pharmaceutical composition can be prepared for decreasing the LDL/HDL cholesterol ratio in the plasma of a mammal which comprises isoniazid together with a pharmaceutically acceptable excipient. Such excipients include for example amylan, acacia, tragacanth, sodium stearate glycolate, elcema, talc and calcium stearate. As discussed above, various hypolipidemic drugs can be included in the composition. The composition is preferably in an oral form. Typical doses of isoniazid are in the range of

10-300 mg accumulated dose. In the event that isoniazid is administered together with hypolipidemic drugs, the dose can be reduced.

The use of isoniazid in the treatment of hyperlipoproteinemia can provide a major contribution to the primary and secondary (post cardiovascular event) prevention of cardiovascular events, including myocardial infarction, cerebrovascular disease and peripheral vascular disease.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been thus far described, but rather the scope of the present invention is limited only by the following claims:

CLAIMS:

1. A method for decreasing the low-density lipoprotein/high-density lipoprotein (LDL/HDL) cholesterol ratio in the plasma of a mammal comprising administering isoniazid to said mammal.

2. A method according to claim 1 wherein said ratio is decreased by an increase in the concentration of HDL cholesterol in the plasma.

3. A method according to claim 2 wherein said ratio is further decreased by decreasing the concentration of LDL cholesterol in the plasma.

4. A method according to claim 1 comprising administering isoniazid together with fibric acids.

5. A method according to claim 4 wherein said fibric acids are selected from the group consisting of clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate.

6. A method according to claim 1 comprising administering isoniazid together with HMG CoA reductase inhibitors.

7. A method according to claim 6 wherein said HMG CoA reductase inhibitors are selected from the group consisting of mevastatin, lovastatin, simvastatin and pravastatin.

8. A method according to claim 1 comprising administering isoniazid together with nicotinic acid to said mammal.

9. Isoniazid for use in the decrease of the LDL/HDL cholesterol ratio in the plasma of a mammal.

10. Isoniazid for use in the decrease of the LDL/HDL cholesterol ratio in the plasma of a mammal according to claim 9 whereby the ratio is decreased by increasing the concentration of HDL cholesterol in the plasma.

11. Use of isoniazid in the preparation of a pharmaceutical composition for use in decreasing the LDL/HDL cholesterol ratio in the plasma of a mammal.

12. A use according to claim 11 wherein said ratio is decreased by increasing the concentration of HDL cholesterol in the plasma.

13. A use according to claim 11 wherein said medicament further comprises fibric acids.

14. A use according to claim 11 wherein said medicament further comprises HMG CoA reductase inhibitors.

15. A use according to claim 11 wherein said medicament further comprises nicotinic acid.

16. A pharmaceutical composition for use in decreasing the LDL/-HDL cholesterol ratio in the plasma of a mammal comprising isoniazid and a pharmaceutically acceptable excipient.

17. A method for treating hyperlipoproteinemia in a mammal comprising administering isoniazid to said mammal.

AMENDED CLAIMS

[received by the International Bureau on 25 August 1997 (25.08.97);
original claims 1, 2, 9 - 12 and 16 amended;
remaining claims unchanged (2 pages)]

1. A method for increasing the concentration of HDL cholesterol in the plasma of a mammal comprising administering isoniazid to said mammal.

2. A method according to claim 1 wherein the low-density lipoprotein/high-density lipoprotein (LDL/HDL) cholesterol ratio in the plasma is decreased as a result of the increase in the concentration of HDL cholesterol in the plasma.

3. A method according to claim 2 wherein said ratio is further decreased by decreasing the concentration of LDL cholesterol in the plasma.

4. A method according to claim 1 comprising administering isoniazid together with fibric acids.

5. A method according to claim 4 wherein said fibric acids are selected from the group consisting of clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate.

6. A method according to claim 1 comprising administering isoniazid together with HMG CoA reductase inhibitors.

7. A method according to claim 6 wherein said HMG CoA reductase inhibitors are selected from the group consisting of mevastatin, lovastatin, simvastatin and pravastatin.

8. A method according to claim 1 comprising administering isoniazid together with nicotinic acid to said mammal.

9. Isoniazid for use in the increase of the concentration of HDL cholesterol in the plasma of a mammal.

10. Isoniazid for use in the increase of the concentration of HDL cholesterol according to claim 9 wherein the LDL/HDL cholesterol ratio is decreased by increasing the concentration of HDL cholesterol.

11. Use of isoniazid in the preparation of a pharmaceutical composition for use in increasing the concentration of HDL cholesterol in the plasma.

12. A use according to claim 11 wherein the LDL/HDL cholesterol ratio in the plasma of a mammal is decreased by increasing the concentration of HDL cholesterol in the plasma.

13. A use according to claim 11 wherein said medicament further comprises fibric acids.

14. A use according to claim 11 wherein said medicament further comprises HMG CoA reductase inhibitors.

15. A use according to claim 11 wherein said medicament further comprises nicotinic acid.

16. A pharmaceutical composition for use in increasing the concentration of HDL cholesterol in the plasma of a mammal comprising isoniazid and a pharmaceutically acceptable excipient.

17. A method for treating hyperlipoproteinemia in a mammal comprising administering isoniazid to said mammal.

## Statement under Article 19(1)

The amendment of the claims is based on making original Claim 2 the main claim and original Claim 1 a dependent claim. The claimed invention is based on the surprising discovery that isoniazid causes an increase in the concentration of HDL cholesterol in the plasma of a mammal. This discovery is not disclosed in any of the references cited in the Search Report.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 97/00085

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 //(A61K31/44,31:215),(A61K31/44,31:19),(A61K31/44, 31:35),(A61K31/44,31:22),(A61K31/44,31:44)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | CAN. J. BIOCHEM. (1972), 50(1), 32-4<br>CODEN: CJBIAE,<br>1972, XP000654503<br>KUTTY, K. M. ET AL: "Serum cholinesterase activity in hyperlipidemia and the in vitro effect of isoniazid on serum cholinesterase" | 1,3,<br>9-12,16,<br>17 |
| Y | see the whole document<br>--- | 2,4-15 |
| Y | DRUG CHEM. TOXICOL. (1977) (1991), 14(3), 293-303 CODEN: DCTODJ;ISSN: 0148-0545,<br>1991, XP002032797<br>KARTHIKEYAN, S. ET AL: "Effect of subacute administration of isoniazid and pyridoxine on lipids in plasma, liver and adipose tissues in the rabbit"<br>see the whole document<br>---<br>-/-- | 2,9-12 |

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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| 24 June 1997 | 02.07.97 |
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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|---|---|---|
| Y | JAMES E. E. REYNOLDS: "MARTINDALE THE EXTRA PHARMACOPOEIA" 1993 , THE PHARMACEUTICAL PRESS , LONDON XP002032798 PAGES 984-994 AND 1045-1056 ----- | 4-8, 13-15 |

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